Haemophagocytosis in bone marrow aspirates in patients with COVID-19

A 78-year-old man with haemorrhagic signs (epistaxis and purpura) presented with severe thrombocytopenia, lymphopenia and circulating neutrophil precursors. A bone marrow aspirate showed increased plasma cells and an increase in pleomorphic megakaryocytes, consistent with peripheral thrombocytopenia. A few macrophages showing haemophagocytosis were also revealed (Fig 1A). Considering the outbreak of COVID-19,[1,2] the combination of thrombocytopenia, lymphopenia and neutrophil precursors led to consideration and detection of SARS-CoV-2, although the patient did not have fever, cough, dyspnoea, diarrhoea, myalgia or headache. The diagnosis was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) assay and chest X-ray (CXR). Apart from thrombocytopenia and haemophagocytosis, this patient did not have other features of secondary haemophagocytic lymphohistiocytosis (sHLH). Clinical and laboratory features of the H-score[3] were not met (Table I). Numerous large megakaryocytes in the bone marrow aspirate and the presence of platelet antibodies led to a diagnosis of autoimmune thrombocytopenic purpura (ITP), potentially related to COVID-19.[4] The platelet count increased after treatment with intravenous immunoglobulin (from 6 to 87 $\times$ 10^9/l in 5 days). Corticosteroids were avoided in the context of COVID-19.[5]

Two other patients with severe COVID-19 confirmed by RT-PCR also had haemophagocytosis demonstrated in a bone marrow aspirate performed for cytopenia (Fig 1B,C). One of them (patient 2) was a 67-year-old obese woman with worsening of her general state, cough and fever, with a known SARS-CoV-2 contact. On admission, she had dyspnoea and tachycardia. CXR showed diffuse bilateral

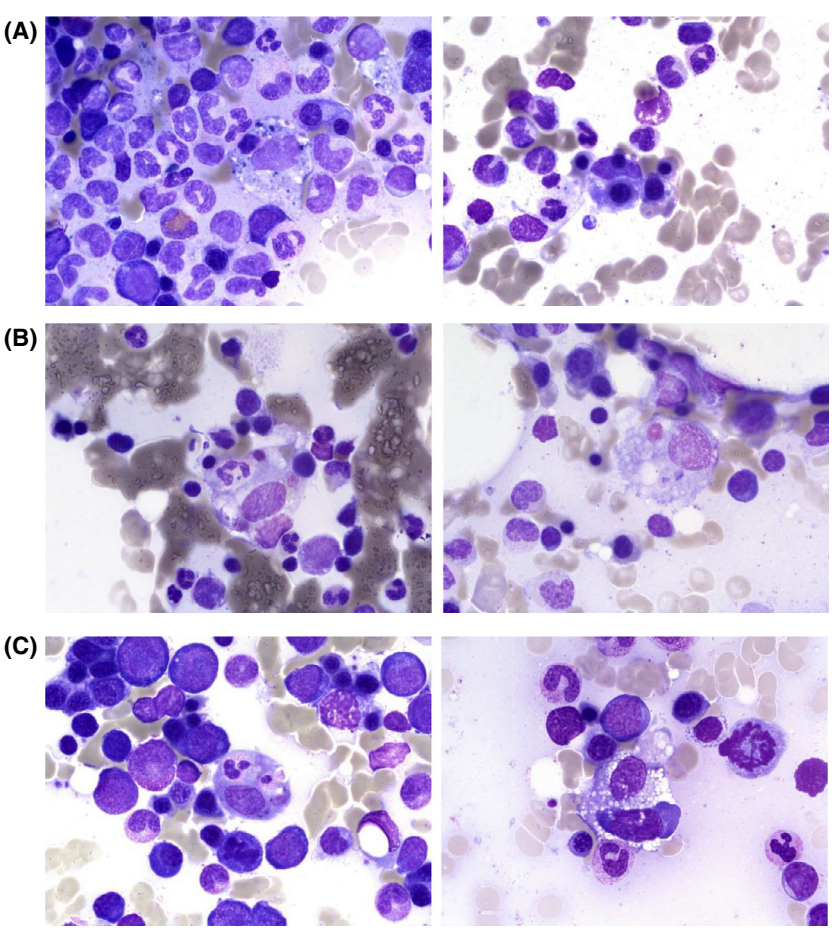

Fig 1. Haemophagocytosis in bone marrow aspirate. May–Grünwald–Giemsa staining of bone marrow aspirate shows histiocytes with engulfed nucleated cells or platelet.

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Table I. Demographic, clinical characteristics and laboratory findings.

Characteristic	Patient 1	Patient 2	Patient 3
Demographic and clinical characteristics			
Age (year)	78	67	63
Sex	Male	Female	Male
Body mass index kg/m^2	27	49	36
Disease features at onset	Epistaxis, asthenia, anorexia	Worsening of the general state, cough, dyspnoea, fever	Worsening of the general state, cough, dyspnoea, hypoxaemia, fever
Imaging features	Diffuse bilateral pulmonary infiltrates	Diffuse bilateral pulmonary infiltrates	Diffuse bilateral pulmonary infiltrates
H-score parameters			
Fever	No	No	Yes
Hepatomegaly	No	No	No
Splenomegaly	No	No	No
Haemoglobin (g/l)	124	104	85
Leucocyte count ($\times10^9$/l)	5·84	12·65	23·65
Platelet count ($\times10^9$/l)	<5	26	89
Serum ferritin (μg/l)	624	620	4899
Triglycerides (mmol/l)	1·35	1·15	5·62
Fibrinogen (g/l)	6·6	1·6	2·1
Aspartate aminotransferase (units/l)	25	87	127
Known underlying immunosuppression	No	No	No
Haemophagocytosis in bone marrow	Yes	Yes	Yes
H-Score	35	84	207
Probability of sHLH (%)	<1	<1	92
Other laboratory findings			
Neutrophil count ($\times10^9$/l)	7·09	9·34	20·81
Lymphocyte count ($\times10^9$/l)	0·8	1·77	0·95
Monocyte count ($\times10^9$/l)	0·57	0·97	0·24
Neutrophil precursors count ($\times10^9$/l)	0·14	0·38	1·65
C-reactive protein (mg/l)	12	204	357
LDH (Units/l)	219	584	588
PT (%)	82	61	99
aPTT (sec)	32·7	35·9	28·4
D-Dimer (mg/l)	2177	>25 000	17 994

sHLH, secondary haemophagocytic lymphohistiocytosis; C-reactive protein, CRP; LDH, lactate dehydrogenase; PT, prothrombin time; aPTT, activated partial thromboplastin time.

pulmonary infiltrates, and SARS-CoV-2 infection was confirmed by RT-PCR. A bone marrow aspirate also revealed increased pleomorphic megakaryocytes and increased plasma cells, but with more prominent haemophagocytosis in this case (Fig 1B). Interestingly, haemophagocytosis often involved platelets. The H-score (Table I) showed a low probability of sHLH (<1%). The patient died of refractory acute respiratory distress syndrome (ARDS). Patient 3 was a 63-year-old obese man with the same symptoms as patient 2 at disease onset. He was hospitalised in the intensive care unit for respiratory and renal failure. A bone marrow aspirate performed for cytopenia showed, once again, increased pleomorphic megakaryocytes, increased plasma cells and numerous haemophagocytic macrophages (Fig 1C). The high H-score probability of 92% as well as the multiorgan failure leading to death confirmed a sHLH diagnosis in this setting.

Discussion

COVID-19 may show varying presentation.[6] Our report highlights the presence of haemophagocytosis in these three cases of COVID-19 presenting with different clinical features and severity: one ITP, one ARDS and one sHLH. Haemophagocytosis is neither necessary nor mandatory for the diagnosis of sHLH.[7] The H-score,[3] including underlying immunoinsufficiency, body temperature, organomegaly, cytopenias, serum ferritin, triglycerides, fibrinogen and aspartate aminotransferase should be taken into account. Cytopenia, hyperferritinaemia and coagulopathy are described in many severe COVID-19 pneumonia cases, suggesting that a subgroup of cases may have a macrophage activation syndrome.[8] In COVID-19, the lungs are mainly involved, and the classical organomegaly pattern of sHLH is uncommonly

reported.[9,10] Paradoxically, we found haemophagocytosis in the bone marrow aspirates of the two patients without features of sHLH. One of these patients did not have evidence of inflammation (low C-reactive protein; see Table I). The macrophage activation in the bone marrow could partially explain the cytopenia in patient 2, with severe thrombocytopenia and activated macrophages engulfing mainly platelets. Furthermore, an autoimmune process may be involved, as in patient 1 with ITP.

Apart from these pathophysiological considerations, in laboratory practice haemophagocytosis in the bone marrow is usually observed in infection, autoimmune disease, myeloproliferative neoplasms, bone marrow failure and haemolysis.[11] Henceforth, whatever the clinical presentation, SARS-CoV-2 infection should be considered among the causes when haemophagocytosis is observed, probably even outside the context of a pandemic.

Author contributions

A.D. and I.H. performed data analysis. A.D. wrote the first draft. I.H., B.D. and J.Y.M. reviewed the manuscript. J.M., P.A., G.L., A.M., M.L. and K.K. provided patient care and data. All the authors reviewed the manuscript and provided final approval.

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